ORIGINAL ARTICLE 10.1111/j.1469-0691.2005.01168.x

Surveillance of chronic haemodialysis-associated infections in southern Israel

J. Gilad[1,2], S. Eskira[1], F. Schlaeffer[2], M. Vorobiov[3], A. Marcovici[3], D. Tovbin[3], M. Zlotnik[3] and A. Borer[1]

[1]Infection Control Unit, [2]Infectious Disease Institute and [3]Department of Nephrology, Soroka University Medical Center and the Faculty for Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

ABSTRACT

During a 12-month surveillance period, haemodialysis (HD) patients in southern Israel were categorised according to the type of vascular access site (VAS), i.e., arteriovenous (AV) fistula, synthetic AV graft, and cuffed or non-cuffed vascular catheters. Endpoints, expressed as cases/100 patient-months, were: incidence of hospital admission; antibiotic therapy; bloodstream infection (BSI); and VAS infection. These were compared to Centers for Disease Control (CDC) surveillance data, overall and by VAS type. In total, 2568 patient-months were analysed. The VAS distribution differed significantly from CDC data for fistulas (72% vs. 31%), grafts (12% vs. 41%), cuffed catheters (11% vs. 25%) and non-cuffed catheters (5% vs. 3%) ($p < 0.0001$ in all cases). Of 151 admissions, 32% resulted from infection, for which 112 antibiotic courses (22% vancomycin) were given. There were 16 BSIs, three involving resistant strains. The incidences of admission, antibiotic therapy, BSI and VAS infection were significantly lower overall, compared to CDC rates, as were most VAS-specific endpoints. These differences may be explained by VAS type distribution, although other factors may also be involved. Reporting regional or national surveillance data may allow a standardised comparison of the incidence of HD-associated infections.

Keywords Antibiotic resistance, catheter, chronic, haemodialysis, infection, resistance

Original Submission: 23 November 2004; **Revised Submission:** 12 January 2005; **Accepted:** 25 January 2005

Clin Microbiol Infect 2005; 11: 547–552

INTRODUCTION

Millions of patients worldwide are being treated with haemodialysis (HD) as a result of chronic end-stage renal disease. HD patients are at high risk of infection because of impaired immune status, severity of illness and frequent puncture of the vascular access site (VAS) during HD [1]. Infections among HD patients may lead to substantial morbidity and mortality, with increased utilisation of healthcare resources and related costs. In addition, antibiotic use may be increased in the HD setting, leading to the emergence of antibiotic-resistant bacteria, including vancomycin-resistant staphylococci [2] and enterococci [3].

Corresponding author and reprint requests: J. Gilad, Department of Internal Medicine E, Soroka Medical Center, PO Box 151, Beer-Sheva 84101, Israel
E-mail: giladko@bgumail.bgu.ac.il

For the above reasons, routine surveillance of HD-associated infections is important; indeed, such surveillance is currently taking place in many countries, including the USA, in which a national surveillance network for HD patients was instituted in 1999 [4]. However, there are no data regarding the incidence of HD-associated infections in Israel. Therefore, the aim of this study was to present the results of regional surveillance of HD-associated infections in southern Israel.

PATIENTS AND METHODS

During the 12-month period October 2002-September 2003, all adult HD patients treated at the Soroka University Medical Center (SUMC) were included in a prospective surveillance study. This institution is a tertiary-care referral centre providing HD services for the entire population of the Negev area (> 500 000 inhabitants). All dialysed patients were Negev area residents.

Surveillance was performed by an infection control nurse. Data were collected as census (denominator), expressed as patient-months, and incidents (numerators), including occurrence of hospital admission (and its cause), occurrence of infections (by anatomical site), infection associated with antibiotic-resistant bacteria, and antibiotic use. Infections (urinary tract infection, pneumonia, wound infection, bloodstream infection (BSI), VAS infection and fever without source) were diagnosed according to Centers for Disease Control (CDC) definitions [4]. Data regarding the clinical indication for HD, as well as underlying medical disorders, were collected from medical records for each dialysed patient.

Patients were categorised according to the type of VAS, namely arteriovenous (AV) fistulas (created from native vessels), synthetic AV grafts, and cuffed (permanent) or non-cuffed (temporary) vascular catheters. The risk for admission caused by infection was analysed according to the type of VAS.

Statistical significance was determined using the chi-square and two-tailed Fisher's exact tests, as appropriate. A p value of < 0.05 was considered statistically significant. Odds ratios were calculated for significant variables. Rates of admission and infection were compared with the data reported by the CDC [4]. Main endpoints were the incidence of hospital admission, need for intravenous antibiotic therapy, incidence of BSI and incidence of VAS infection.

RESULTS

Between 199 and 224 HD patients were dialysed each month, with a total of 2568 patient-months. The mean age of the study patients was 63.5 ± 15 years (median 68 years; range 15–89 years) and 55.2% were males. The clinical indications for HD were: diabetic nephropathy (39%), hypertensive nephropathy (17%), secondary glomerulonephritis (10%), idiopathic glomerulonephritis (6%), atherosclerosis (6%), renal amyloidosis (3%), polycystic kidney disease (3%), renal vasculitis (3%), nephrocalcinosis (2%), reflux nephropathy (2%), obstructive uropathy (1%) and interstitial nephritis (1%). Diagnosis of underlying kidney disease remained uncertain in 7% of cases.

Underlying medical disorders among study patients were: dyslipidaemia (50%), diabetes mellitus (48%), ischaemic heart disease (44%), arterial hypertension (38%), diabetic foot (21%), congestive heart failure (21%), cardiac arrhythmias (18%), chronic hepatitis C virus infection (15%), valvular heart disease (10%), severe anaemia (10%), chronic lung disease (9%), previous stroke (5%) and malignancy (5%). Other more rare diagnoses (affecting $< 2\%$) were present in 20% of the patients. These included systemic amyloidosis, inflammatory bowel disease, various autoimmune and collagen vascular diseases, and thyroid and parathyroid disorders.

The distribution of the census according to the type of VAS is shown in Table 1. Fistula was the most common VAS among the study patients. Compared to the CDC census data, HD patients at SUMC were significantly more likely to be dialysed using fistula (and to a lesser, but significant, extent using non-cuffed catheters), and were significantly less likely to be dialysed using grafts or cuffed catheters.

During the study period, 151 HD patients were admitted. Admitting wards were nephrology (64.2%), internal medicine (24.5%), general surgery (2.7%), gynaecological surgery (2.7%) and other (5.9%). Most (68%) admissions were associated with non-infectious disorders, including cardiovascular problems as well as non-infectious VAS problems (Table 2). Of admissions resulting from infection (32%), most (76.6%) were associated with fever, but without an infectious focus present at admission, while there was a distinct infectious focus in 23.4% (comprising 7.3% of overall admissions) of cases. VAS infection accounted for 2% of admissions (or 6.4% of admissions caused by infection).

BSI (either VAS-related or BSI associated with another source) was detected in 16 cases (10.6% of admissions), of which 12 were monomicrobial

Table 1. Number of patient-months (denominator) according to vascular access site at the Soroka University Medical Center, compared with data from the Centers for Disease Control [4]

VAS type	SUMC (%)	CDC (%)	p value/OR
Fistula	1855 (72.2)	23 340 (30.9)	< 0.0001/5.8
Graft	300 (11.7)	30 844 (40.9)	< 0.0001/0.19
Cuffed catheter	274 (10.7)	18 959 (25.1)	< 0.0001/0.36
Non-cuffed catheter	122 (4.7)	2342 (3.1)	< 0.0001/1.56
Total	2568 (100%)	75 535 (100%)	–

VAS, vascular access site; SUMC, Soroka University Medical Center; CDC, Centers for Disease Control and Prevention; OR, odds ratio.

Table 2. Diagnoses at admission of study patients (n = 151)

Diagnosis	Frequency
Infectious	
Fever without source	24%
VAS infection	2%
Non-VAS wound infection	3%
Pneumonia	1%
Urinary tract infection	2%
Non-infectious	
Other diagnoses (non-infectious)	44%
Cardiovascular events	10%
VAS problem (non-infectious)	14%

VAS, vascular access site.

infections and four were polymicrobial. Overall, 21 microorganisms were isolated from BSI cases, of which 57.2% were Gram-positive bacteria, 38.3% Gram-negative bacteria, and 4.5% yeasts (Table 3). Three BSI cases involved antibiotic-resistant pathogens, i.e., methicillin-resistant *Staphylococcus aureus* (MRSA) and multiresistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (both susceptible only to carbapenems and polymyxin). All Gram-positive isolates were vancomycin-susceptible.

The incidence rates (cases/100 patient-months) for the study endpoints were 5.9 for hospital admissions, 2.5 for intravenous antibiotic therapy, 0.6 for BSI and 0.1 for VAS infection (Table 4). Compared to CDC data, this study population had a significantly lower incidence of hospital admission, intravenous antibiotic therapy, BSI and VAS infection.

VAS-specific incidence rates for the study endpoints are shown in Table 4. The incidence of hospitalisation was significantly lower in SUMC compared to the CDC census for all types of VAS. The incidence of intravenous antibiotic therapy was similar, except for a significantly lower incidence in SUMC patients dialysed using cuffed catheters. SUMC patients dialysed using a fistula or cuffed catheters had a significantly lower incidence of BSI. Moreover, all VAS, except for grafts, were associated at SUMC with a significantly lower incidence of VAS infection.

Table 3. Species distribution of pathogens isolated from the blood of haemodialysis patients at Soroka University Medical Center (n = 21)

Species	Frequency (%)
Methicillin-susceptible *Staphylococcus aureus*	28
Coagulase-negative *Staphylococcus* spp.	13
Escherichia coli	14
Methicillin-resistant *Staphylococcus aureus*	10
Acinetobacter baumannii	10
Enterococcus faecalis	5
Pseudomonas aeruginosa	5
Proteus spp.	5
Enterobacter cloacae	5
Candida albicans	5

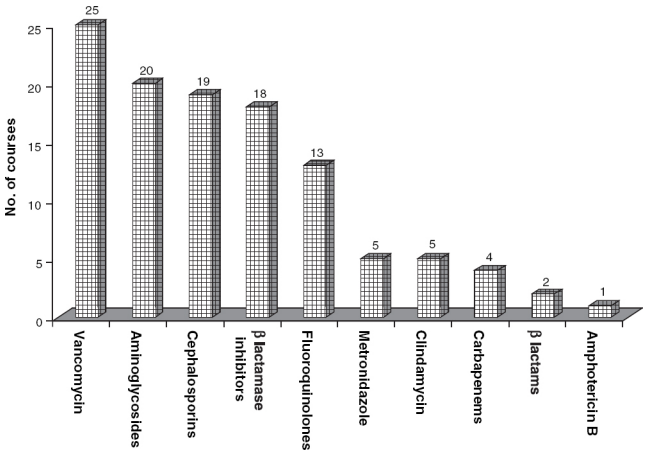

Fig. 1. Antibiotics given to haemodialysis patients.

Antibiotic utilisation among study patients is depicted in Fig. 1. In total, 112 antibiotic courses were given to 65 admitted patients. One course was given to 33 patients, two courses to 17 patients, and three courses to 15 patients. Vancomycin was given to 22% of patients, and 38% received a β-lactam (cephalosporin, β-lactamase inhibitor-containing preparation or carbapenem).

DISCUSSION

The number of HD patients in the USA has increased sharply during the past 30 years. In 1999, >3000 HD centres had >190 000 HD patients and >60 000 staff members [5]. HD patients are at risk of infection because of the requirement for vascular access for prolonged periods, and repeated opportunities for cross-transmission of pathogens person-to-person or

Table 4. Comparison of incidence rates (cases/100 patient-months) at Soroka University Medical Center with data from the Centers for Disease Control [4]

	Fistula			Graft			Cuffed catheter			Non-cuffed catheter			All types		
Incident	SUMC	CDC	p value/OR	SUMC	CDC	p value/OR	SUMC	CDC	p value/OR	SUMC	CDC	p value/OR	SUMC	CDC	p value/OR
Denominator	1867	23 333	–	302	30 903	–	276	18 928	–	123	2371	–	2568	75 535	–
Hospital admission	4.55	9.4	< 0.001/0.46	4.33	12.9	< 0.001/0.3	10.5	20.5	< 0.001/0.45	19.5	32	0.003/0.5	5.9	14.3	< 0.001/0.05
Antibiotic therapy	1.7	2	0.35	1.66	2.4	0.4	4.3	7.9	0.03/0.53	1.3	7.8	0.06	2.5	3.8	0.007/0.65
BSI	0.16	0.5	0.032/0.31	0	0.95	0.12	2.17	5.8	0.01/0.36	5.7	9.95	0.12	0.6	2.3	< 0.001/0.26
VAS infection	0.05	0.56	0.003/0.1	0.33	1.36	0.2	0.36	8.4	< 0.001/0.04	0	12	< 0.001/ < 0.01	0.1	3.2	< 0.001/0.04

SUMC, Soroka University Medical Center; CDC, Centers for Disease Control and Prevention; BSI, bloodstream infection; VAS, vascular access site; OR, odds ratio.

via contaminated devices, equipment and supplies. Furthermore, HD patients are immunosuppressed and require frequent hospitalisation and surgery, which increases exposure to nosocomial infections.

The annual mortality rate among HD patients is 23%. Infections are the second most common cause of mortality, accounting for 15% of deaths [5], with sepsis being the most common infectious cause of mortality. Several studies have shown that BSI occurs in 0.63–1.7% patients/month, and VAS infections (with or without BSI) in 1.3–7.2% patients/month [6–9]. Among French HD patients, 28% of 230 HD-associated infections involved the VAS [6]. Thus, the VAS may be the most common site for infection, and can cause disseminated BSI or loss of vascular access.

The present study evaluated the incidence of HD-associated infection in our institution by means of the same surveillance method applied by the CDC in the USA. The overall incidences of hospital admission, intravenous antibiotic therapy, BSI and VAS infection at SUMC were significantly lower than those reported by the CDC. There may be several possible explanations for these findings.

First, underlying diseases are among the most important risk factors for HD-associated infections. Therefore, differences in the case-mix may account for differences in study endpoints. The present study population was typical of developed countries, with diabetic nephropathy ranking first among the indications for HD (nearly 40% of cases). However, CDC census data do not include the prevalence of underlying diseases and dialysis indications, and therefore it is impossible to rule out any influence of intrinsic risk factors for HD-associated infections.

Second, the type of VAS has the greatest influence on bacterial infectious morbidity in HD patients, with catheters posing the highest risk for infection, grafts intermediate risk, and native AV fistulas the lowest risk [8]. A study in the USA has shown that, compared to AV fistula, the risk of VAS infection was 2.2 with AV grafts, 13.6 with cuffed catheters, and 32.6 with non-cuffed catheters [10]. Similar differences are also evident from CDC data [4] and available recommendations [5]. These data support the guidelines issued in 2001 by the National Kidney Foundation [11]. These guidelines, which have been adopted worldwide, suggest that at least 40% of HD patients should have a native AV fistula, and that <10% of HD patients should be dialysed via vascular catheters for >3 months without a maturing permanent VAS.

Most (> 70%) SUMC patients were treated by fistula, compared to 31% of CDC patients. The respective rates for vascular catheters were 15.4% and 28.2%. Whereas fistulas appear to be the major type of VAS used in Europe and Japan, AV grafts are still the preferred VAS in the USA [12]. As of December 2001, fistulas comprised 30.4% of VASs in the USA, but this number represents an increase from lower rates (*c.* 22%) documented 5 years earlier, before the implementation of the National Kidney Foundation guidelines [13]. In addition, of 18 HD networks surveyed by the CDC, only two had a fistula prevalence of >40% [13]. These differences accentuate the need to consider VAS-specific infection rates while performing surveillance, as overall infection rates may over- or underestimate the need for an infection control intervention in the HD population.

Comparison of VAS-specific incidence rates from the SUMC and CDC data revealed several trends. First, the incidence of hospital admission was significantly lower in SUMC for every given VAS. Second, for cuffed catheters only, the incidence of intravenous antibiotic therapy was significantly lower in SUMC patients; a lower incidence, but not significantly so, was shown with other types of VAS. Therefore, it can be speculated that the lower incidence of hospitalisation (but not antibiotic therapy) is the result of different admission policies or a different incidence of non-infectious disorders. Alternatively, inappropriate antibiotic use may explain a similar incidence of antibiotic administration in spite of the lower incidence of hospitalisations. The high rate of fever in this study cohort without an infectious focus (*c.* 77%) supports this possibility.

Third, a significantly lower incidence of BSI and/or VAS infection was observed for the SUMC patients with fistulas, cuffed catheters and non-cuffed catheters, but not for those with grafts. The lower incidence of VAS-specific BSI and VAS infection suggests that other factors (besides distribution of VAS type), either intrinsic (as discussed previously) or extrinsic (e.g., infection control practices), may have influenced the risk of infection in this patient population. HD patients dialysed using grafts represent a subset of

patients for whom further efforts to prevent infection may be worthwhile in this institution.

VAS infections are caused mainly by Gram-positive bacteria, especially staphylococci and enterococci [5]. HD patients have played a prominent role in the epidemic of vancomycin resistance, and have been reported to comprise up to one-quarter of hospitalised patients infected or colonised with vancomycin-resistant *Enterococcus* spp. [14,15]; indeed, HD patients were the most prominent risk group among the first identified cases of vancomycin intermediately-resistant *S. aureus* [16]. Other resistant pathogens isolated from HD patients include MRSA and multiresistant Gram-negative non-fermentative bacilli [5].

Vancomycin is used commonly in HD patients [17], as it can be administered conveniently to patients during HD treatments, even though reasonable alternatives exist [18]. The present study showed that vancomycin is used frequently (*c.* 25% of antibiotic courses) in SUMC for HD patients admitted with suspected infection. However, in retrospect, vancomycin therapy was completely appropriate in only two cases (of MRSA BSI). BSI caused by MRSA comprised 12.5% of BSI cases, 4% of admissions with suspected or proven infection, and 1.3% of overall admissions. Therefore, routine empirical use of vancomycin in this patient population seems unjustified. Failure to use vancomycin appropriately may result in the selection of glycopeptide-resistant Gram-positive bacteria [19]. Optimisation of the antibiotic policy for infected HD patients is required, given that empirical anti-staphylococcal therapy with cefazolin may prove to be an adequate alternative and has been recommended previously in this setting [5]. Empirical vancomycin therapy should be reserved for patients at high risk of MRSA infection (e.g., those known to be colonised with MRSA) or in life-threatening situations.

There are few data regarding HD-associated infection in Israel. Only one recent paper has focused on HD-associated infections; 67 HD patients with BSI were compared to non-HD BSI patients in a case-control study [20], which evaluated the influence of HD on the risk-factors, bacteriology and outcome of bacteraemic patients. Current surveillance data from Israeli hospitals are lacking, even though the CDC have advocated periodic surveillance of HD-associated infections [5].

In conclusion, surveillance of HD-associated infections in southern Israel revealed significantly lower incidences of hospital admission, intravenous antibiotic therapy, BSI and VAS infection compared to CDC data. These differences may be attributed, at least in part, to the different distribution of VAS types (a high rate of AV fistulas and a low rate of vascular catheters) in this study population. The observed differences in VAS-specific incidents may be related to intrinsic or extrinsic factors and warrant further study. The present study highlights the importance of reporting regional and national HD-associated infection surveillance data, especially VAS-specific incidents, as comparisons of general incidence with international benchmarks may be hampered by differences in population characteristics.

ACKNOWLEDGEMENTS

This work was presented in part at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, September 2003, Chicago, IL, USA.

REFERENCES

1. Horl WH. Neutrophil function and infections in uremia. *Am J Kidney Dis* 1999; **33**: xlv–xlvii.
2. Fridkin S. Vancomycin-intermediate and -resistant *Staphylococcus aureus*: what the infectious disease specialist needs to know. *Clin Infect Dis* 2001; **32**: 108–115.
3. Montecalvo MA, Shay DK, Patel P *et al.* Bloodstream infections with vancomycin-resistant enterococci. *Arch Intern Med* 1996; **156**: 1458–1462.
4. Tokars JI, Miller ER, Stein G. New national surveillance system for hemodialysis-associated infections: initial results. *Am J Infect Control* 2002; **30**: 288–295.
5. Centers for Disease Control and Prevention. Recommendations for preventing transmission of infections among chronic hemodialysis patients. *MMWR* 2001; **50**: 1–63.
6. Kessler M, Hoen B, Mayeux D, Hestin D, Fontenaille C. Bacteremia in patients on chronic hemodialysis: a multicenter prospective survey. *Nephron* 1993; **64**: 95–100.
7. Bonomo RA, Rice D, Whalen C, Linn D, Eckstein E, Shlaes DM. Risk factors associated with permanent access-site infections in chronic hemodialysis patients. *Infect Control Hosp Epidemiol* 1997; **18**: 757–761.
8. Hoen B, Paul-Dauphin A, Hestin D, Kessler M. EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol* 1998; **9**: 869–876.
9. Stevenson KB, Adcox MJ, Mallea MC, Narasimhan N, Wagnild JP. Standardized surveillance of hemodialysis vascular access infections: 18-month experience at an outpatient, multifacility hemodialysis center. *Infect Cont Hosp Epidemiol* 2000; **21**: 200–203.

10. Stevenson KB, Hannah EL, Lowder CA *et al*. Epidemiology of hemodialysis vascular access infections from longitudinal infection surveillance data: predicting the impact of NKF-DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 2002; **39**: 549–555.
11. Anonymous. NKF-K/DOQI Clinical Practice Guidelines for Vascular Access: update 2000. *Am J Kidney Dis* 2001; **37**(suppl 1): S137–S181.
12. Rayner HC, Besarab A, Brown WW, Disney A, Saito A, Pisoni RL. Vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS): performance against Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines. *Am J Kidney Dis* 2004; **44**(suppl 3): 22–26.
13. Tokars JI, Finelli L, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2001. *Semin Dial* 2004; **17**: 310–319.
14. Shay DK, Maloney SA, Montecalvo M *et al*. Epidemiology and mortality risk of vancomycin resistant enterococcal bloodstream infections. *J Infect Dis* 1995; **172**: 993–1000.
15. Stroud L, Edwards J, Danzig L, Culver D, Gaynes R. Risk factors for mortality associated with enterococcal blood stream infections. *Infect Cont Hosp Epidemiol* 1996; **17**: 576–580.
16. Centers for Disease Control and Prevention. *Staphylococcus aureus* with reduced susceptibility to vancomycin—Illinois, 1999. *MMWR* 1999; **48**: 1165–1167.
17. Green K, Schulman G, Haas DW, Schaffner W, D'Agata EM. Vancomycin prescribing practices in hospitalized chronic hemodialysis patients. *Am J Kidney Dis* 2000; **35**: 64–68.
18. Fogel MA, Nussbaum PB, Feintzeig ID, Hunt WA, Gavin JR, Kim RC. Cefazolin in chronic hemodialysis patients: a safe, effective alternative to vancomycin. *Am J Kidney Dis* 1998; **32**: 401–409.
19. Berns JS. Infection with antimicrobial-resistant microorganisms in dialysis patients. *Semin Dial* 2003; **16**: 30–37.
20. Shmuely H, Pitlik S, Yahav J, Samra Z, Leibovici L. Seven-year study of bacteremia in hospitalized patients on chronic hemodialysis in a single tertiary hospital. *Renal Failure* 2003; **25**: 579–588.